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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,918	03/27/2001	Arthur M. Krieg	C1039/7048 (AWS)	4953

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EXAMINER
MINNIFIELD, NITA M

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,918	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-11 and 13-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-11 and 13-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 13, 2006 has been entered.

2. Applicants' amendment filed February 13, 2006 is acknowledged and has been entered. Claims 1, 4-11 and 13-30 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below. This is a NON-FINAL Office action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 4-11 and 13-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/817165. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim and disclose methods of treating dermatitis or allergic reactions comprising administering to the subject a composition comprising an

immunostimulatory oligonucleotide or immunostimulatory oligonucleotide and allergen.

It is also noted that Applicants have filed numerous related applications and that there could potentially be other double patenting rejections. Applicants are encouraged to apprise the Examiner of all applications that claim the same or similar subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This provisional obviousness-type double patenting rejection is maintained for the reasons of record. Applicant's arguments filed ***May 19, 2005*** have been fully considered but they are not persuasive. Applicants have stated that they are willing to consider filing a terminal disclaimer, if necessary, at the time that claims are deemed to be otherwise in condition for allowance. Applicants also note that both the instant application and Application No. 10/817,165, which is a divisional of the instant application, currently claim priority to the same parent application, filed July 15, 1994. This rejection is maintained until a properly filed terminal disclaimer has been filed.

This provisional rejection is maintained for the reasons of record. In the amendment filed February 13, 2006, Applicants stated that they are willing to consider filing a terminal disclaimer, if necessary, at the time that claims in the instant application are deemed to be otherwise in condition for allowance.

5. Claims 1, 4-11 and 13-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating asthma (murine model) comprising administering to a subject in need of such treatment an immunostimulatory oligonucleotide (8-100 nucleotides long) comprising SEQ ID

NO: 10, does not reasonably provide enablement for the ability to treat atopic dermatitis or allergic dermatitis comprising administering to a subject in need of such treatment any immunostimulatory oligonucleotide (8-100 nucleotides long) having the claimed formula as shown in claims 1 or 5, or the broad scope of the possible CpG-ODN that are envisioned in the formulas of claims 1 or 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The claims are directed to a method of treating atopic dermatitis or allergic dermatitis comprising administering to a subject in need of such treatment a composition comprising a CpG oligonucleotide (8-100 or 8-40 nucleotides long) or a comprising a CpG oligonucleotide and allergen. The CpG oligonucleotide formulas are $X_1CG\ X_2$ or $X_1\ X_2CGX_3X_4$. The claims, for example, define that X_1, X_2, X_3, and X_4 are any nucleotide. The routes of administration have been defined as well as specific CpG sequences, SEQ ID NO: 37-40, 42-45.

The specification discloses Example 12 (see p. 51), prevention of the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma. Mice were immunized with *Schistosoma mansoni* eggs (SEA) by i.p. injection on days 0 and 7. SEQ ID NO: 10 was administered to the immunized mice and soluble SEA was administered by intranasal instillation on days 14 and 21. After challenge the mice were sacrificed and cytokine levels and other assays conducted on the lavage fluids. The specification indicates that Figures 9-15 show that CpG/SEA induced inflammatory cells, eosinophils, to be present and generated macrophages; higher IL-12 was induced, IL-4 was reduced and IFN-gamma production increased. Applicants assert that the CpG redirected

the cytokine response of the lung to production of IFN-gamma, indicating a Th1 type immune response (p. 52).

The specification does not teach that any of the other myriad of possibilities of CpG having the claimed formulas can be used to treat any form of dermatitis, atopic or allergic. The results shown for asthma do not indicate that the CpG will function in the same manner to treat atopic dermatitis or allergic dermatitis.

The state of the art is unpredictable with regard to treatments using CpG. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms (See Krieg et al, Weiner and McCluskie et al for recent advances using CpG oligonucleotides). Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (See McCluskie et al in its entirety, and especially on page 296; see Krieg et al on page 524). Weiner states furthermore that the molecular mechanisms of CpG oligonucleotides' immuno-stimulatory effects are not yet understood (See especially page 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (See Agrawal et al especially on pages 78-80; see pages 31-32 of the instant specification). Hussain et al 2004 also teaches that the "[C]ombined data from our studies with the murine model of allergic rhinitis and limited data from skin favor the idea that CpG ODN may be an attractive therapy in the treatment of acute atopic dermatitis. On the other hand, chronic AD skin has significantly fewer IL-4 and IL-13 mRNA-expressing cells but higher numbers of IL-5, GM-

CSF, IL-12, and IFN-γ mRNA expression than has acute AD skin (Leung, 1999). For that reason, the long-term benefits of treatment with CpG ODN remain speculative." (see p. 27, col. 1). Further, Satoh et al teaches that CpG-ODN is responsible for worsening of allergic contact dermatitis. "S.c. applied Cpg ODN one day before sensitization of naïve mice significantly enhanced the ACD to DNFB which showed severe edema with massive CD8+ T cell infiltration." (abstract) Satoh et al also teaches that "[T]hese results indicate that CpG ODN vaccinations may elicit and aggravate side effects such as harmful CD8+ T cell-mediated type IV hypersensitivity responses." (abstract) Dziadzio et al teaches that "[V]arious combinations of plasmid DNA, immunostimulatory oligonucleotide (ISS-ODN), and proteins have been studied in murine models to evaluate the effectiveness of DNA vaccination. The success in skewing the immune response towards a Th1 phenotype in mice still needs to be evaluated in humans. The use of DNA vaccination as a treatment for allergic disease remains a viable option for the future." (abstract) The state of the art, taken as a whole, is still unpredictable with regard to the use of ISS-ODN in treating atopic dermatitis or allergic dermatitis in a subject (human or otherwise) in need of such treatment.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward a method of treating the claimed atopic dermatitis or allergic dermatitis comprising the administration of any immunostimulatory nucleic acid comprising the formulas claimed in claims 1 and 5, for example. As previously stated the specification teaches an increase in immunomodulation in mice (and comprising conversion from a Th2 to a Thl immune response), and treatment of asthma in a mouse model

comprising the administration of SEQ ID NO: 10. One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of atopic dermatitis or allergic dermatitis in any organism comprising the administration by any route of any immuno-stimulatory nucleic acid comprising the formulas in claims 1 and 5 in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects provided *in vivo* in any and/or all organisms upon administration via any route of CpG containing oligonucleotides, and further whereby treatment effects are provided in any and/or all organism for atopic dermatitis or allergic dermatitis. The breadth of the claims is very broad and the quantity of experimentation required is undue. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms, and further whereby treatment effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment of the claimed atopic dermatitis or allergic dermatitis comprising administration by any route of any CpG containing oligonucleotide (claimed formulas), and since determination of these factors for a particular CpG containing oligonucleotide and for the particularly claimed conditions, route of administration and organism is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

The examples provided of the induction of various interleukins in spleen, liver or thymus cells are not representative of the successful treatment of any atopic condition (i.e. atopic dermatitis or allergic dermatitis) using any CpG containing oligonucleotide. No correlation is taught in the instant disclosure between the ability of these CPG containing oligonucleotides to induce a Th1 response in vitro (e.g. amount of IL-6 induction) and their ability to treat a representative number of atopic conditions (i.e. atopic dermatitis or allergic dermatitis) in vivo. An assumed common mechanism of action does not ensure enablement for treatment. Effective delivery to appropriate and concentration of a particular CPG containing oligonucleotide necessary for providing treatment effects for a particular CPG containing sequence are still highly unpredictable. The success of treating asthma with SEQ ID NO: 10 is not necessarily representative or correlative of the ability to successfully treat any atopic condition (i.e. atopic dermatitis or allergic dermatitis) with the generic sequences claimed. The in vivo treatment success for these generic sequences require undue experimentation beyond that provided in the instant disclosure.

The rejection is maintained for the reasons of record. Applicant's arguments filed ***August 23, 2004*** have been fully considered but they are not persuasive. It is noted that Applicants arguments have been previously addressed, see above rejection.

The rejection is maintained for the reasons of record. Applicant's arguments filed ***May 19, 2005*** have been fully considered but they are not persuasive. Applicants have asserted that the claims as currently amended all relate to methods for the treatment of atopic dermatitis and that atopic dermatitis is recognized by those skilled in the art to be a major form of eczema that is distinct from allergic contact dermatitis (ACD). For example, ACD is believed to be mediated primarily by CD8+ cytotoxic T cells in a Type IV delayed-type hypersensitivity reaction.

Akiba H et al. (2004) J Invest Dermatol 123:488-93. In contrast, atopic dermatitis is believed to represent primarily a (CD4+) Th2-related disorder characterized by increased IgE levels, eosinophilia, and IL-4- and IL-5-secreting Th2-type cells in the peripheral blood and Th2-skewed cytokine gene expression and eosinophilia in skin lesions, particularly acute skin lesions. Leung DYM (1999) J Allergy Clin Immunol 104:599-108 The examples of exacerbation of 2,4-dinitrofluorobenzene (DNFB)-induced ACD by local (but not systemic) injection of CpG ODN described in Akiba H et al. and Satoh M et al., are thus not relevant to the claims because they relate to ACD rather than to atopic dermatitis. However, it is noted that Kussebi et al (Current Med. Chem. – Anti-Inflammatory & Anti-Allergy Agents, 2003, 2:297-308) teaches that "[D]ifferences in control of life span was observed between peripheral blood activated memory/effector T cells and T cells infiltrating the eczema lesions in atopic and non-atopic diseases. In peripheral blood of atopic dermatitis patients both $CD4^+$ and $CD8^+$ subsets of activated memory/effector T cells expressed upregulated Fas and Fas-ligand and undergo spontaneous activation induced cell death." (p. 304, col. 1) Applicants have stated that Table 5 on page 27 of the specification shows induction of the Th1 cytokines using several different oligonucleotides. However, the data in Table 5 were obtained from in vitro studies that indicate that Th1 cytokines levels were increased in cells incubated with the listed oligonucleotides, it is not clear that the tested oligonucleotides would function in the same manner in an in vivo situation. As previously stated not all CpG oligonucleotides function in the same manner in all organisms and biological systems and some of these oligonucleotides have a negative effect. Applicants have called the Examiner's attention to a 1.132 declaration of Joel Kline that was submitted September 10, 2003, which Applicants have asserted sets forth "…original experimental data showing that CpG oligo-nucleotides were effective in the treatment of atopic dermatitis in a mouse model. Specifically, mice treated with intraperitoneal (i.e., systemic) injections of CpG-ODN 1826 (corresponding to SEQ ID NO:10 in the instant application) dramatically reduced skin eosinophilia as compared to control animals not treated with CpG. In addition, the experiments described in the declaration specifically demonstrate that treatment with CPG-ODN 1826 was effective in treating both asthma and atopic dermatitis. Thus the results shown for asthma do indicate that CpG oligonucleotides effective for treating asthma also function to treat atopic dermatitis and that a common mechanism of action strongly supports enablement for the claimed method for treatment of atopic dermatitis." (Remarks, p. 9) However, it is not clear that the experimental data shown in the declaration was achieved following any of the protocols set forth in the pending specification. The

Examiner cannot evaluate whether these results support the conclusions asserted by Applicants. Which protocols from the specification were used? It is not clear that these data enable the pending claims and specification. Applicants have stated that the mechanism of action of CpG-ODN and TLR9 as a receptor not withstanding, in the context of this assertion of unpredictability it is submitted that the Weiner 2000 reference ("we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG DNA") is not relevant. Applicants have asserted that it is not necessary to know the mechanism and that only a little experimentation is needed to enable the full scope of the claims. It should be noted that the specification and claimed invention should be enabled at the time of filing, not at some point in the distant future. The state of the art post-filing as well as the specification indicate that the scope and breath of the claimed invention is not enabled. The claims contemplate a myriad of possible oligonucleotides having the CG motif and range in size from 8-40 or 8-100 nucleotides. The specification has not shown that the myriad oligonucleotides contemplated by the claims will function in a method that treats atopic dermatitis in a subject. An assumed common mechanism of action does not ensure enablement for treatment. Effective delivery to appropriate and concentration of a particular CPG containing oligonucleotide necessary for providing treatment effects for a particular CPG containing sequence are still highly unpredictable. SEQ ID NO: 10 contains 2 traditional CpG motifs, each of the CpG dinucleotides are flanked 5' by two purines and flanked 3' by two pyrimidines. The success of treating atopic dermatitis with SEQ ID NO: 10 is not necessarily representative or correlative of the ability to successfully treat any atopic condition or atopic dermatitis with the generic sequences claimed. The in vivo treatment success for these generic sequences would require undue experimentation beyond that provided in the instant disclosure. Therefore, the instant scope of enablement rejection under 112, 1 paragraph is maintained.

The rejection is maintained for the reasons of record. Applicant's arguments filed February 13, 2006 have been fully considered but they are not persuasive. Applicants have urged the examiner to appreciate how the *in vivo* results disclosed for asthma, as well as additional *in vivo* and *in vitro* results disclosed in the specification, support the claimed methods for treating atopic dermatitis.

Applicants have referred to Tables 1-3 and Table 5 stating that these tables establish that unmethylated CpG is responsible for the immune stimulation (tables 1-3) and that the immune stimulation has the characteristic pattern of a Th1 response. Applicants also discuss the leading theory of asthma ("Hygiene Hypothesis") in 1996. That being, "...exposure to infectious organisms or exposure to antigens derived from these pathogenic organisms induce a T-helper 1 (Th1) response early in life, shifting the immune response of individuals with an allergic predisposition away from a T-helper 2 (Th2) response and towards a Thl response (IL-12, lFN-γ), thereby conferring protection from developing asthma. It would have been believed that the synthetic CpG-containing oligonucleotides described in the instant application can invoke Thl responses mimicking what occurs in nature, via infectious agents, to confer protection against asthma." (p. 5 of Remarks) Applicants have asserted that Example 12 of the specification "...confirmed that a CpG-containing oligonucleotide would have the ability to initiate in vivo a pattern of cytokine release which would drive the immune system toward Th1 response and would treat asthma." (p. 6 of Remarks) Applicants have asserted that because the CpG-containing oligonucleotide effects a shift away from a Th2 immune response it would be expected to be useful for treating not only asthma but also any atopic condition including dermatitis; and that because the CpG-containing oligonucleotide effects a shift towards a Th1 immune response it would be expected to be useful for treating not only asthma but also any atopic condition including dermatitis. However, it is noted that this is scope of enablement rejection with regard to the use of the broad scope of any and all immunostimulatory oligonucleotides as set forth in the independent claims as well as the fact that none of the examples set forth specific enablement for the specific

treatment of atopic dermatitis, which is now claimed. Is the specific induction of a Th1 response and the suppression of a Th2 response specifically indicative of successful treatment of atopic dermatitis? The induction of a Th1 response is indicative of success for numerous treatmentsfor example treatment of bladder cancer (see Luo et al Cytokine, 2003, 21:17-26).

The Examiner acknowledges that McCluskie et al refrence is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines) and the pending independent claims include limitations that exclude plasmid vectors (e.g. upper size limit of 100 nucleotides).

Applicants have asserted that each of the references (Krieg et al 2000, Weiner et al 2000, Satoh et al 2002, Agrawal et al 2000, Dziadzio et al) cited to show that the state of the art is unpredictable with regard to the claimed method actually shows promise, may be a promising, probable successful use in humans, potential and/or suggestion of the claimed invention and its enablement. It is noted that even though these references may suggest the possibility of CpG's usefulness, they still also indicate even several years after Applicants' effective filing date that the scope of the use of the claimed composition is not enabled. Further, Weiner cautions that despite therapeutic promise of some CpG ODNs, all CpG ODNs are not alike and more needs to be learned about the heterogenous responses that occur based on host organism, cell subset or CpG ODN sequence. Weiner teaches that the clinical effects of CpG ODN have not yet been explored and further work with the immunostimulatory nucleic acids in both the laboratory and the clinic are needed before their true promise as investigational immunological and therapeutic agents is known. It is also noted Krieg et al mentions (as recited in the Remarks)

that CpG is a more effective Th1-like adjuvant that complete Freund's and that CpG has been used as an adjuvant in allergy vaccines. The pending claims do not recite the administration of any antigen (allergen or otherwise) and therefore the teaching of Krieg et al seem to suggest that it would be unlikely that the claimed method would be successful with regard to treating atopic dermatitis.

Applicants have asserted that numerous working examples were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims. Consistent with the descriptions, a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. For instance, US Patent Application Serial No. 10/644,052 corresponding to PCT Publication No W02004/016805 (copy previously submitted) describes numerous examples of CpG oligonucleotides that stimulate an immune response. However, 10/644052 is evidence of enablement post filing; the specification must be enabled at the time of filing, particularly in view of the unpredictable state of the art regarding the claimed invention. Further, were the experimental protocols set forth in 10/644052, specifically Examples 22, 25 and 26, the same manner as the experimental protocols of the pending application?

The amount of direction or guidance presented in the specification and the absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward the claimed invention. One skilled in the art would not accept on its face in view of the lack of examples given in the specification as being representative of the successful

treatment of atopic dermatitis in view of the lack of guidance in the specification and the known unpredictability associated with the ability to predict the biological effects exerted by the numerous CpG pilognucleotides encompassed by the claims. The specification as filed fails to provide particular guidance which resolves the known unpredictability disclosed in the state of the art. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the claimed oligonucleotides. Since the specification fails to provide particular guidance for the treatment of atopic dermatitis and the art teaches that this is not yet possible (i.e. highly unpredictable), it would require undue experimentation to practice the invention as presently claimed.

It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed *in vivo* method.

The claimed invention must be enabled as of the filing date of the patent application, not enabled by publications post filing. Whether the specification would have been enabling as of the filing date involves consideration of the nature

of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b).

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. 35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used. (see MPEP 2164.05(a))

The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already

available to the public. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If

individuals of skill in the art state that a particular invention is not possible years after the filing date that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled.

Further, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In re Angstadt, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of

inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

6. No claims are allowed.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

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Art Unit 1645

NMM
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